Medical Staff Conference

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Pancreatic Diarrheal Syndromes

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been our custom to ask each chief medical resident to speak at Medical Grand Rounds at the end of his year in this capacity. We are most appreciative of the leadership that Dr. Hayden Klaeveman has brought to this position. He has had a continuing interest in the subject of gastrointestinal hormones and will review for us today the diarrheal syndromes associated with disorders of the pancreatic islet cells.*

DR. KLAEVEMAN:† In 1958 Verner and Morrison described two cases of profuse intractable watery diarrhea associated with severe hypokalemia in a noninsulin-secreting islet cell tumor of the pancreas.[1] In the first reported patients, in contrast to patients with the Zollinger-Ellison syndrome, achlorhydria was present, leading to the acronym WDHA syndrome (standing for watery diarrhea, hypokalemia and achlorhydria). In the 17 years since this initial report, some 50 patients with this devastating disorder have been described and in the ensuing years it has become apparent that achlorhydria is not necessarily an integral part of the syndrome. In fact, in most patients there is normal or decreased gastric acid secretion leading to application of the term "pancreatic cholera" to this syndrome. Considered in terms of hormonally mediated pancreatic disorders, these patients represent approximately 5 percent of nonbeta islet cell tumors of the pancreas.

The outstanding feature in these patients is diarrhea of variable severity and duration, generally of a progressive nature. In most patients, the symptoms have been present for three to four years before diagnosis. In its fulminant form, the diarrheal stool has the appearance of weak tea and contains little formed substance, while in the more quiescent form the stools take on a mushy consistency. The stool is inoffensive and there is no blood present. Abdominal cramping is sometimes present while weight loss is inevitably seen. Nausea and vomiting may occur in the more fulminant episodes.

As the diarrhea progresses, symptoms due to hypokalemia and dehydration appear. The patient may complain of generalized muscle weakness and even paralysis, and may even show signs of impending stupor.

During the attacks the serum potassium concentration frequently is less than 2 mEq per liter

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
AMP = adenosine monophosphate
APUD = amine precursor uptake, decarboxylation
G17 = heptadecapeptide gastrin
GLI = enteroglucagon
GIP = gastric inhibitory polypeptide
MEA = multiple endocrine adenomatosis
MSH = melanocyte-stimulating hormone
PGE_1 = prostaglandin type E_1
VIP = vasoactive intestinal polypeptide
WDHA = watery diarrhea, hypokalemia and achlorhydria
ZES = Zollinger-Ellison syndrome

and is always less than 3 mEq per liter. Fecal water losses average 5 liters per day and fecal potassium losses are 200 to 400 mEq per day during attacks. Loss of bicarbonate leads to the features of hypokalemic acidosis. Azotemia results from dehydration and hypokalemic nephropathy.

In general, findings on roentgenographic studies, stool cultures, sigmoidoscopy, stool fat determinations and urinary 5-HIAA (hydroxyindoleacetic acid) concentration studies are normal. Steatorrhea, if present, is mild.

Gastric acid secretion ranges from normal to histamine-fast achlorhydria. Peptic ulcer disease is not a feature of this syndrome.

There are other interesting and unusual features of this syndrome.

- Decreased glucose tolerance with or without overt diabetes mellitus occurs in approximately 50 percent of patients. Glucose metabolism frequently returns to normal after successful tumor resection. It has not been established whether the tumor secretes a hormone with hyperglycemic actions or whether the improved tolerance is due to correction of hypokalemia.

- Hypercalcemia occurs in approximately 50 percent of the patients and, like the impaired glucose tolerance, it may be abolished by tumor resection. In one series of four patients in whom hypercalcemia and watery diarrhea syndrome were present, parathyroid adenoma was shown in only one patient, and the true frequency of hyperparathyroidism is probably much less than this. Multiple endocrine adenomatosis syndromes are unusual in these patients. Consequently, neck exploration in these patients should be postponed until the effect of resection of the pancreatic tumor on calcium metabolism can be assessed.

- Cutaneous flushing of head and neck has been observed in approximately 20 percent of patients with the syndrome and again has resolved with successful tumor resection. There has been no other evidence of carcinoid syndrome and no evidence of abnormal metabolism of serotonin, or other vasoactive amines.

Other less frequently observed aberrations have included: gallbladder disease with stones in six patients, an enlarged gallbladder filled with dilute bile rich in bicarbonate and chloride in several patients.

The diagnosis should be suspected in patients with documented chronic watery diarrhea, hypochlorhydria and hypokalemia in whom the carcinoid syndrome, small and large bowel lesions (for example, villous adenomas), malabsorption of bile salts or nutrients or both, bacterial and parasitic infections, extrapancreatic neoplasms (for example, medullary carcinoma of the thyroid) and laxative abuse have been excluded. Pancreatic scanning and celiac arteriography have been of little help in delineating the tumor.

The treatment is primarily surgical with either extirpation of the tumor or, if the pancreas appears normal, diagnostic distal pancreatectomy, as 80 percent of the lesions are in the body and tail of the pancreas. If this is not curative and microscopic study shows diffuse hyperplasia, only total pancreatectomy is curative in the absence of metastatic disease.

In 53 reported cases to date, 30 percent of patients have been cured by removal of a benign tumor. In another 13 percent of these patients the diagnosis was not suspected antemortem, and at postmorten examination all had surgically resectable benign tumor. Diffuse hyperplasia was present in 20 percent, and in 8 of 11 patients, or 73 percent of these, surgical resection was curative. In 37 percent of these patients, malignant tumors with metastases were present, and only two patients benefitted from surgical operation. Therefore, 75 percent of patients with WDHA syndrome have been, or could have been, cured by surgical procedures.[2]

It is for those unfortunate patients with metastatic disease that other modes of therapy are required. One patient has been cured by radio-

therapy, and the administration of adrenocorticosteroids has afforded temporary relief in others (however, steroid therapy may lead to release of gastric secretory inhibition with resultant peptic ulceration).

Of chemotherapeutic regimens, one patient has been successfully treated with 5-fluorouracil. Most recently two patients with metastatic islet cell tumors have been treated with the antitumor antibiotic streptozotocin which is selectively toxic to pancreatic islet cells by inhibition of pyridine nucleotide synthesis. In both patients, there has been a salutory response to therapy (for 12 and 13 months respectively) after intra-arterial administration of the drug. It remains to be seen whether this remission will be maintained.[3]

Next I would like to turn to a consideration of the etiologic agent in this syndrome. The cell line which gives rise to these tumors appears to be that of the APUD (amine precursor uptake, decarboxylation) cells which constitute an endocrine system in the epithelium of the gastrointestinal tract, pancreas, bile ducts and bronchi. The embryologic origin of these cells is unclear—some hold that the APUD cells are of entodermal (foregut) origin, whereas others propose that they derived from neural crest tissue and therefore are neuroendocrine in origin.

In addition to serotonin, APUD cells synthesize polypeptide hormones, including gastrin, secretin, glucagon, vasoactive intestinal polypeptide (VIP), enteroglucagon (GLI) and probably other hormones. Because the WDHA syndrome is associated with APUD cell proliferation it might be expected that cell proliferation in organs other than the pancreas might give rise to the syndrome. This is supported by a recent report on four patients with bronchogenic carcinoma in whom WDHA was associated with an increased plasma VIP concentration.[4]

Of the candidate hormones which might produce this syndrome, the leading culprit is VIP followed by secretin and then gastric inhibitory polypeptide (GIP). Of 30 patients with the disorder studied by Said, in 25 there were increased plasma levels of VIP.[4] Bloom and associates have reported increased concentration of this peptide in plasma, tumor, or both, in another six patients with WDHA.[5] On the other hand, Kraft and Zollinger have been the major proponents of the secretin hypothesis, which is based on early observations by Gardner that both secretin and extracts of WDHA tumors caused inhibition of water and electrolyte transport *in vitro*. These authors have observed secretin-like activity in sera from certain patients with pancreatic cholera.[6] However, several studies have failed to show increased pancreatic water and bicarbonate secretion in patients with pancreatic cholera.

VIP and secretin have certain structural similarities, sharing 9 of 28 amino acids in common. Furthermore, virtually every tissue which responds to secretin responds in a similar fashion to VIP.

Actions of VIP include vasodilation (flushing), inhibition of histamine and pentagastrin stimulated acid secretion (achlorhydria), stimulation of electrolyte and water secretion by the pancreas, gallbladder relaxation (dilated gallbladder), stimulation of small intestinal secretion and stimulation of glycogenolysis (abnormal glucose tolerance test). Animal studies have shown that VIP, like prostaglandin type E_1 (PGE_1) and cholera toxin, stimulates small bowel adenylate cyclase, increases intracellular cyclic adenosine monophosphate (AMP), and produces net secretion of fluid and electrolytes in isolated ileal mucosa. Furthermore, VIP, but not secretin, stimulates human small intestinal adenylate cyclase.[7]

However, in the two patients reported by the group at the National Institutes of Health, increased activity of adenylate cyclase was not found in small bowel biopsy studies, nor were increased serum VIP concentrations, but intracellular cyclic AMP was not measured.

Lastly, Elias and co-workers have reported one patient with WDHA in whom positive immunofluorescence was noted in a tumor when an antisera against GIP was used.[8]

To summarize, the etiologic agents in WDHA syndrome are as yet unidentified. The leading candidate is VIP, but in several patients an increase in VIP concentrations in plasma was not found. There are at least two possible explanations for this: (1) Except for gastrin, radioimmunoassays for gastrointestinal hormones are not widely available or are poorly standardized; (2) since the APUD cell system produces a gamut of potential culprits, more than one hormone might produce the same clinical constellation.

Zollinger-Ellison Syndrome

In the time remaining, I will briefly discuss the other hormonally mediated pancreatic diarrheogenic syndrome. The syndrome of fulminant peptic ulcer disease with recurrences despite repeated

gastric operations, gastric hypersecretion and nonbeta islet cell tumors of the pancreas was first described in 1945, but it was Zollinger and Ellison in 1955 who first suggested that a hormone from the tumor was responsible for the disease.[9] It has now been established beyond reasonable doubt that the polypeptide gastrointestinal hormone gastrin is present in abundant quantities in the tumors and in the circulation of patients with the Zollinger-Ellison syndrome (ZES) and that the pathophysiologic events that characterize the Zollinger-Ellison syndrome represent consequences of excess circulating gastrin. It has been proposed that in analogy to insulin-containing insulinomas the term "gastrinoma" be applied to the tumors.[10]

Clinical Manifestations

• *Incidence.* The true incidence of ZES has not been established, nor is the true frequency of Zollinger-Ellison tumors among patients with peptic ulcer disease known. At present, there are more than 1,000 reported cases. It is probable that gastrinomas are present in less than 1 percent of patients with the diagnosis of peptic ulcer disease.

• *Age and sex.* The reported age range for patients with ZES is from 7 years to 90 years with a mean age of onset between the third and fifth decade of life. Sixty percent of the patients are male, although there is probably no sexual predominance.

• *Symptoms.* Abdominal pain is the most common presenting complaint, being present in 70 to 95 percent of patients. The location and quality of pain may be similar to that of uncomplicated peptic ulcer disease, or may be severe and relentless. By the time of diagnosis, symptoms have been present in most patients for more than one year.

In their review of 260 cases, Ellison and Wilson reported that in 93 percent of patients, peptic ulcer disease was present and in 7 percent, diarrhea without peptic ulceration was present.[11] They reported pain related to peptic ulcer disease in 74 percent, pain related to diarrhea in 15 percent, pain related to perforation in 18 percent, melena in 22 percent, hematemesis in 19 percent, diarrhea in 36 percent and vomiting in 26 percent.

Diarrhea has been reported in a third to three quarters of patients with ZES, and is responsive to treatment by gastric aspiration, as well as by total gastrectomy. The diarrhea is due principally to the presence of excess gastric acid secreted into the upper gastrointestinal tract. In addition, pentagastrin has been shown to reduce the absorption of water in the human proximal small intestine. However, since correction of acid hypersecretion by aspiration or gastrectomy corrects the diarrhea, it is unlikely that the direct hormonal effects of gastrin are major factors responsible for diarrhea.

Abnormal small bowel morphology has been described in patients with ZES, including gastrin metaplasia, submucosal edema and hemorrhage, abnormal villi and cellular infiltration of the lamina propria. Rapid transit is a common radiologic finding in patients with ZES, but the mechanism is unknown.

In summary, the diarrhea of Zollinger-Ellison syndrome is caused by multiple factors, including (1) delivery of excess acid to the duodenum, (2) damage to the small bowel mucosa by gastric acid, (3) decreased small bowel absorption resulting from the action of gastrin and from mucosal damage and (4) hypermotility.

Steatorrhea is frequently found in patients with ZES. However, the precise frequency of this abnormality has not been established. Steatorrhea is a consequence of irreversible inactivation of pancreatic lipase at low duodenal pH and precipitation of glycine conjugated bile salts at acid pH —thus decreasing their availability for micelle formation.

In 10 to 40 percent of patients with Zollinger-Ellison syndrome, there are associated nonpancreatic endocrine tumors, being termed multiple endocrine adenomatosis (MEA) type I or Wermer's syndrome. Hyperparathyroidism is the most commonly associated endocrine abnormality. Pituitary, adrenal, thyroid and ovarian tumors are less common.

In a review by Ballard of patients with type I MEA, parathyroid abnormalities were present in 88 percent, with pancreatic and pituitary abnormalities in 85 and 65 percent respectively. A 19 percent incidence of adrenal and thyroid disorders was found.[12]

Rarely an islet cell tumor may produce multiple hormones, such as adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), glucagon and insulin.

It has been observed in several patients that correction of hyperparathyroidism by resection of one or more adenomas notably improved symptoms of peptic ulcer disease, and decreased gastric acid secretion when ZES was also present.

Pathology

Immunohistochemical techniques have been successful in demonstrating gastrin in islet cells of the normal pancreas. Gastrin-containing granules have been localized to cells found in the periphery of the pancreatic islets. These cells have staining characteristics of delta cells. Of interest, although the highest concentration of immunoreactive gastrin is found in the gastric antrum, to date only one case of a gastrinoma of the stomach has been reported. The majority of gastrinomas are located in the pancreas or duodenum.

Recently Polak and co-workers have proposed the possible existence of two types of Zollinger-Ellison syndrome. In patients with ZES type I, there are notably elevated serum gastrin levels with antral gastrin cell hyperplasia. Such patients tend to be young, and tend to have a relatively short history of peptic ulcer disease when compared with patients with the "usual" type II ZES with gastrinomas.[13]

Physical Examination

There are no diagnostic physical findings in Zollinger-Ellison syndrome. Patients may show weight loss, epigastric tenderness and signs of hypermotility. Tumor masses are rarely palpable.

X-ray Studies

Findings on barium studies of the upper gastrointestinal tract are almost always abnormal. It has been suggested that the diagnosis of Zollinger-Ellison syndrome is primarily the radiologist's responsibility.

Radiographic examination of the stomach frequently shows excess gastric juice in the stomach and large gastric folds due to mucosal hyperplasia. Occasionally a large atonic stomach and rarely an isolated gastric ulcer is found.

The most common abnormality of the duodenum, seen in approximately 75 percent of patients with Zollinger-Ellison syndrome, is an ulcer in the duodenal bulb or immediate postbulbar area. Other duodenal findings include evidence of duodenitis with blunted valvulae conniventes, and irregularity of the duodenal wall, with dilation of the duodenal lumen.

The radiographic findings in the jejunum are similar to those in the duodenum. The presence of distal duodenal or proximal jejunal ulcers is highly suggestive of Zollinger-Ellison syndrome, but occur only in approximately 22 percent of cases.

Angiography has been useful in showing pancreatic lesions, but is positive in less than a third of cases. Similarly, success in showing gastrinomas with selenomethionine scanning has been low.

Gastric Secretion

The principal laboratory finding which suggests the diagnosis of Zollinger-Ellison syndrome is gastric acid hypersecretion, especially in the basal state. The two measurements of acid secretion which appear to give the best indication of ZES are the rate of basal acid secretion and the ratio of basal to peak stimulated acid secretion, or acid concentration.

The criteria applied to basal acid secretion in patients with intact stomachs are: (1) Twelve-hour overnight secretion of greater than 100 mEq of hydrochloric acid (HCl), and (2) one-hour basal secretion of greater than 15 mEq of HCl.

Ellison and Wilson reported 74 percent of patients with ZES secreted greater than 100 mEq of HCl overnight. However, 3 percent of patients with peptic ulcer disease secreted acid at this rate, and a third of patients with ZES failed to meet this criterion.

The ratio of basal to peak stimulated acid secretion (BAO:MAO) of greater than 0.6 has been found in approximately 60 percent of patients with ZES. However, there are reports of up to 15 percent of normals who have ratios of greater than 0.6.

Measurements of acid secretion in the stomachs of patients after operation may produce varied results due to variable recovery of acid and contamination by alkaline reflux from the upper small intestine. It has been suggested that greater than 5 mEq per hour of acid secretion in a patient with previous acid reducing operations should suggest the diagnosis of ZES.

Identification of gastric acid hypersecretion in a patient with peptic ulcer disease now requires serum gastrin measurement by radioimmunoassay to establish the diagnosis of ZES.

Gastrin

Time does not permit a review of the gastrin story which has recently been reviewed. Briefly, several forms of immunoreactive gastrin have been identified.

- There is heptadecapeptide gastrin (G17), which exists in two forms, gastrin I and gastrin II. Gastrin II has a sulfate on the tyrosyl residue in

position 12. The C-terminal tetrapeptide amide possesses the full range of biologic activity of the heptadecapeptide amide.

This form of gastrin predominates in human antral mucosa and in gastrinomas, has a half life of approximately five minutes, and has a greater molar potency than other forms of gastrin. Gastrin is also present in the intestine which has a gradient of concentration with highest values in the proximal duodenum and progressively diminishing concentrations throughout the remainder of the small intestine.

• The major form of gastrin in the circulation is "big gastrin" which has 34 amino acid residues, has sulfated and nonsulfated forms, a longer half life, and longer mode of onset of action. The longer biological half life of big gastrin may explain the relative preponderance of big gastrin in the circulation when compared with its proportionately smaller content in gastrinomas.

The various roles of gastrin are as follows: Stimulation of acid secretion and to a lesser extent pepsin secretion, stimulation of bile flow, inhibition of water and electrolyte absorption in the small intestine, contraction of the gastroesophageal sphincter, relaxation of the sphincter of Oddi, relaxation of the ileocecal sphincter, increase gastric mucosal blood flow, increase incorporation of amino acids into proteins in the gastrointestinal tract, contraction of gastric smooth muscle and release of insulin.

Measurement of gastrin by radioimmunoassay measures larger molecular forms as well as heptadecapeptide gastrin, and shows normal and duodenal ulcer patients to have fasting concentrations between 20 and 150 picograms (pg) per ml. After a protein meal, gastrin increases by 50 to 300 percent during the first hour.

Fasting hypergastrinemia can be found in patients with pyloric obstruction, achlorhydria and hypochlorhydria, gastric atrophy, gastric carcinoma, pheochromocytoma, retained gastric antrum in the afferent loop after gastrojejunostomy, and following vagotomy. Furthermore, patients with ZES can have day-to-day variations in gastrin values that are at times diagnostic and at other times only suggestive.

Consequently, provocative tests have been described to distinguish patients with ZES from those with duodenal ulcers. One is the calcium challenge test: Calcium gluconate is infused over a three-hour period at a rate of 12 to 15 mg of calcium per kg of body weight per hour. In patients with ZES there is a 2- to 3-fold increase in gastrin during the third hour accompanied by an increase in gastric acid secretion to rates similar to those observed with maximal histamine stimulation. Too few patients have been studied to establish strict criteria for ZES, but an absolute increase of greater than 500 pg per ml in serum gastrin is highly suggestive of ZES.

A second and more recently described provocative test for identifying patients with gastrinomas is that of secretin infusion. Secretin in man decreases gastric acid secretion probably by inhibition of both gastrin-mediated gastric secretion and inhibition of gastric release. In normals and patients with duodenal ulcer, secretin (3 units per kg of body weight per hour) lowers serum gastrin, whereas in patients with ZES there is a paradoxical increase in serum gastrin accompanied by acid hypersecretion.

Thus, a profile of serum gastrin concentration, which consists of the following may be described for patients with ZES: (1) elevated fasting serum gastrin concentrations in a patient who usually demonstrates gastric acid hypersecretion (values greater than 1,000 pg per ml are virtually diagnostic, and 200 to 1,000 pg per ml are suggestive), (2) exaggerated gastrin release in response to calcium infusion and (3) paradoxical increase in serum gastrin concentration following intravenous secretin infusion.

Therapy

As a general rule patients with ZES respond poorly to medical therapy. However, there have been no controlled clinical trials. One patient has been successfully treated with gastric irradiation with 2,200 roentgens. Streptozotocin has not proved effective.

The major mode of therapy, therefore, is surgical. In their review of 260 cases of ZES, Ellison and Wilson reported that 60 percent of ZES tumors were malignant and 44 percent were metastatic, with one half of these involving the liver. Only 30 percent of the tumors were identifiable benign adenomata. There was a 10 percent incidence of microadenomata alone. However, in another 9 percent of patients with either benign or malignant tumors microadenomatosis was present.

Of duodenal wall tumors, approximately 50 percent were benign solitary lesions and, therefore, the chance of a duodenal gastrinoma being solitary is greater than for pancreatic gastrinoma.

A more recent survey of the influence of

gastrectomy on survival in malignant gastrinomas reviewed the course of 267 patients.[14] In patients who had total gastrectomy there was a 55 percent five-year survival versus 27 percent survival for patients with lesser gastric procedures. Deaths from progressive tumor growth occurred in 17 percent of patients at risk after total gastrectomy versus 30 percent of patients at risk after lesser gastric surgery.

For patients with liver metastases in whom total gastrectomy was done, there was a 42 percent five-year survival versus 7 percent five-year survival with lesser gastric surgical procedures. Regression of metastatic tumors was clearly documented in only four patients, presumptive regression occurred in seven other patients—in all but two of these eleven patients total gastrectomies were done. In all patients in whom lesser gastric surgical procedures were carried out, the major causes of increased mortality were recurrent peptic ulcer disease and, to a lesser extent, deaths related to progressive tumor growth.

At present, several recommendations regarding therapy of ZES should be followed. (1) If parathyroid adenoma are present, these should be resected before undertaking abdominal surgical operation because pronounced improvement in diarrhea, steatorrhea and ulcer symptoms may occur. (2) If, at surgical operation, an apparently isolated solitary tumor is found without spread to lymph nodes or liver, it should be resected while monitoring gastric acid secretion. If acid secretion falls greatly, no gastric surgical procedures should be done. (3) Total gastrectomy should be done for all other patients. (4) Under no circumstances should total pancreatectomy and subtotal gastrectomy be done. One can never be sure that tumor is limited to the pancreas. If it is not, total gastrectomy will be required later and total gastectomy and total pancreatectomy are virtually incompatible with life.

REFERENCES

1. Verner JV, Morrison AB: Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. Am J Med 25: 374-380, Sep 58

2. Verner JV, Morrison AB: Endocrine pancreatic islet disease with diarrhea. Arch Intern Med 133:492-500, May 1974

3. Kahn CR, Levy AG, Gardner JD, et al: Pancreatic cholera —Beneficial effects of treatment with streptozotocin. N Engl J Med 292:941-945, May 1975

4. Said SL: Vasoactive intestinal polypeptide: elevated plasma and tissue levels in the watery diarrhea syndrome due to pancreatic and other tumors. Clin Res (in press)

5. Bloom SR, Polak JM, Pearse AGE: Vasoactive intestinal peptide and watery-diarrhoea syndrome. Lancet 2:14-16, Jul 1973

6. Tompkins RK, Kraft AR, Zollinger RM: Secretin-like choleresis produced by a diarrheogenic nonbeta islet cell tumor of the pancreas. Surgery 66:131-137, Jul 1969

7. Klaeveman HL, Conlon TP, Levy AG, et al: Effect of gastrointestinal hormones on adenylate cyclase activity in human jejunal mucosa. Gastroenterology 68:667-675, Apr 1975

8. Elias E: Pancreatic cholera due to production of gastric inhibitory polypeptide. Lancet 2:791-793, Oct 1972

9. Zollinger RM, Ellison EH: Primary peptic ulceration of the jejunum associated with islet cell tumors of the pancreas. Ann Surg 142:709-728, Oct 1955

10. Isenberg JL, Walsh JH, Grossman ML: Zollinger-Ellison syndrome. Gastroenterology 65:140-165, Jul 1973

11. Ellison BH, Wilson SD: The Zollinger-Ellison syndrome— Reappraisal and re-evaluation of 260 registered cases. Ann Surg 160: 512-530, Sep 1964

12. Ballard HS, Frame B, Hartsock RJ: Familial mutiple endocrine adenoma peptic ulcer complex. Medicine (Balt) 43:481-516, Jul 1964

13. Polak JM, Stagg B, Pearse AGE: Two types of Zollinger-Ellison syndrome: immunofluorescent, cytochemical, and ultrastructural studies of the antral and pancreatic gastrin cells in different clinical states. Gut 13:501-512, ul 1972

14. Fox PS, Hofmann JW, Decosse JJ, et al: The influence of total gastrectomy on survival in malignant Zollinger-Ellison tumors. Ann Surg 180:558-565, Oct 1974